CLAIMS

What is claimed is:

1. A method for providing an image of an internal region of a patient having a vascular plaque, wherein the method comprises (i) administering to the patient a contrast agent comprising, in an aqueous carrier, targeted vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety; and (ii) scanning the patient using ultrasound to obtain a visible image of the region.

2. A method according to Claim 1 wherein said contrast agent comprises lipid vesicles.

3. A method according to Claim 2 wherein said lipid comprises a phospholipid.

4. A method according to Claim 3 wherein said phospholipid is selected from the group consisting of a phosphatidylcholine and a phosphatidylethanolamine.

5. A method according to Claim 4 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoyl-phosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

6. A method according to Claim 5 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

7. A method according to Claim 4 wherein said phosphatidylethanol-amine is selected from the group consisting of dipalmitoylphosphatidylethanolamine,

dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

8. A method according to Claim 7 wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

9. A method according to Claim 2 wherein said lipid further comprises a polymer.

10. A method according to Claim 9 wherein said polymer comprises a hydrophilic polymer.

11. A method according to Claim 10 wherein said polymer comprises polyethylene glycol.

12. A method according to Claim 1 wherein said vesicles comprise protein vesicles.

13. A method according to Claim 12 wherein said protein comprises albumin.

14. A method according to Claim 1 wherein said gas or gaseous precursor comprises a fluorinated compound.

15. A method according to Claim 14 wherein said fluorinated compound is a perfluorocarbon compound.

16. A method according to Claim 15 wherein said perfluorocarbon is selected from the group consisting of perfluoromethane, perfluoroethane, perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane,

perfluorohexane, perfluoroheptane, perfluorooctane, perfluorononane, perfluorodecane, perfluorodecalin, perfluoroundecane, perfluorododecane, and mixtures thereof.

17. A method according to Claim 16 wherein said perfluorocarbon is selected from the group consisting of perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane, perfluorohexane, and mixtures thereof.

18. A method according to Claim 17 wherein said perfluorocarbon is perfluorobutane.

19. A method according to Claim 1 wherein said targeting ligand comprises a lipid containing said acid moiety.

20. A method according to Claim 19 wherein said targeting ligand comprises an acidic phospholipid.

21. A method according to Claim 20 wherein said targeting ligand is a diacyl phospholipid.

22. A method according to Claim 20 wherein said targeting ligand is selected from the group consisting of phosphatidic acids, phosphatidyl serines and phosphatidylinositols.

23. A method according to Claim 22 wherein said targeting ligand is a phosphatidic acid which is dipalmitoylphosphatidic acid.

24. A method according to Claim 22 wherein said targeting ligand is a phosphatidyl serine which is dipalmitoylphosphatidylserine.

25. A method according to Claim 1 wherein said contrast agent further comprises a low viscosity oil.

26. A method according to Claim 25 wherein said oil is selected from the group consisting of silicone oil, cod liver oil, triacetin, mineral oil, plant oil, oil comprising fluorinated triglycerides, biocompatible saturated fatty acids, biocompatible unsaturated fatty acids, biocompatible partially hydrogenated fatty acids, silicon-based oils, and synthetic oil.

27. A method according to Claim 2 wherein said vesicles are selected from the group consisting of micelles and liposomes.

28. A method according to Claim 27 wherein said lipid vesicles are selected from the group consisting of unilamellar lipid vesicles, oligolamellar lipid vesicles and multilamellar lipid vesicles.

29. A method according to Claim 28 wherein said lipids are in the form of monolayers or bilayers.

30. A method for diagnosing the presence of a vascular plaque in a patient, wherein the method comprises (i) administering to the patient a contrast agent comprising, in an aqueous carrier, targeted vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety; and (ii) scanning the patient using ultrasound to obtain a visible image of any plaque in the patient.

31. A method according to Claim 30 wherein said contrast agent comprises lipid vesicles.

32. A method according to Claim 31 wherein said lipid comprises a phospholipid.

33. A method according to Claim 32 wherein said phospholipid is selected from the group consisting of a phosphatidylcholine and a phosphatidylethanolamine.

34. A method according to Claim 33 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoyl-phosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

35. A method according to Claim 34 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

36. A method according to Claim 33 wherein said phosphatidylethanol-amine is selected from the group consisting of dipalmitoylphosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoylphosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

37. A method according to Claim 36 wherein said phosphatidylethanol-amine comprises dipalmitoylphosphatidylethanolamine.

38. A method according to Claim 31 wherein said lipid further comprises a polymer.

39. A method according to Claim 38 wherein said polymer comprises a hydrophilic polymer.

40. A method according to Claim 39 wherein said polymer comprises polyethylene glycol.

41. A method according to Claim 30 wherein said vesicles comprise protein vesicles.

42. A method according to Claim 41 wherein said protein comprises albumin.

43. A method according to Claim 30 wherein said gas or gaseous precursor is a fluorinated compound.

44. A method according to Claim 43 wherein said fluorinated compound is a perfluorocarbon compound.

45. A method according to Claim 44 wherein said perfluorocarbon compound contains from 1 to about 12 carbons.

46. A method according to Claim 45 wherein said perfluorocarbon compound contains from about 3 to about 6 carbons.

47. A method according to Claim 46 wherein said perfluorocarbon compound contains about 4 carbons.

48. A method according to Claim 30 wherein said targeting ligand comprises a lipid containing said acid moiety.

49. A method according to Claim 48 wherein said targeting ligand comprises an acidic phospholipid.

50. A method according to Claim 49 wherein said targeting ligand is a diacyl phospholipid.

51. A method according to Claim 49 wherein said targeting ligand is selected from the group consisting of phosphatidic acids, phosphatidyl serines and phosphatidylinositols.

52. A method according to Claim 51 wherein said targeting ligand is a phosphatidic acid which is dipalmitoylphosphatidic acid.

53. A method according to Claim 51 wherein said targeting ligand is a phosphatidyl serine which is dipalmitoylphosphatidylserine.

54. A method according to Claim 30 wherein said contrast agent further comprises a low viscosity oil.

55. A method according to Claim 54 wherein said oil is selected from the group consisting of silicone oil, cod liver oil, mineral oil, triacetin, plant oil, oil comprising fluorinated triglycerides, biocompatible saturated fatty acids, biocompatible unsaturated fatty acids, biocompatible partially hydrogenated fatty acids, silicon-based oils, and synthetic oil.

56. A method according to Claim 31 wherein said vesicles are selected from the group consisting of micelles and liposomes.

57. A method according to Claim 56 wherein said lipid vesicles are selected from the group consisting of unilamellar lipid vesicles, oligolamellar lipid vesicles and multilamellar lipid vesicles.

58. A method according to Claim 57 wherein said lipids are in the form of monolayers or bilayers.

59. A method for the therapeutic delivery *in vivo* of a bioactive agent to a region in a patient having a vascular plaque, wherein the method comprises administering to a patient a therapeutically effective amount of a formulation comprising, in combination with a bioactive agent, a composition which comprises vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said

targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety.

60. A method according to Claim 59 wherein said bioactive agent is selected from the group consisting of anti-thrombolytic agents, statins, anti-cancer agents, and radioactive materials.

61. A method according to Claim 60 further comprising applying ultrasonic energy to the patient to release said bioactive agent from said targeted vesicles.

62. A method according to Claim 61, wherein said ultrasonic energy causes said vesicles to rupture.

63. A method according to Claim 59, further comprising the step of scanning the patient with diagnostic imaging to visualize said vesicles at the target site.

64. A method of dissolving plaque in a blood vessel comprising (i) administering to a patient, by intravenous injection, a targeted vesicle composition comprising vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety; (ii) scanning said patient with diagnostic imaging to visualize said plaque; and (iii) applying ultrasonic energy to said plaque.

65. A method according to Claim 64 wherein said ultrasonic energy in step (iii) is pulsed ultrasound.

66. A method according to Claim 64 wherein said targeting ligand comprises a lipid containing said acid moiety.

67. A method according to Claim 66 wherein said targeting ligand comprises an acidic phospholipid.

68. A method according to Claim 67 wherein said targeting ligand is a diacyl phospholipid.

69. A method according to Claim 67 wherein said targeting ligand is selected from the group consisting of phosphatidic acids, phosphatidyl serines and phosphatidylinositols.

70. A method according to Claim 69 wherein said targeting ligand is a phosphatidic acid which is dipalmitoylphosphatidic acid.

71. A method according to Claim 69 wherein said targeting ligand is a phosphatidyl serine which is dipalmitoylphosphatidylserine.

72. A method for providing an image of an internal region of a patient having a vascular plaque, wherein the method comprises (i) administering to the patient a contrast agent comprising, in an aqueous carrier, targeted vesicles formulated from a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety; and (ii) scanning the patient using ultrasound to obtain a visible image of the region.

73. A method for diagnosing the presence of a vascular plaque in a patient, wherein the method comprises (i) administering to the patient a contrast agent comprising, in an aqueous carrier, targeted vesicles formulated from a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety; and (ii) scanning the patient using ultrasound to obtain a visible image of any plaque in the patient.

74. A method for the therapeutic delivery *in vivo* of a bioactive agent to a region in a patient having a vascular plaque, wherein the method comprises administering to a patient a therapeutically effective amount of a formulation comprising, in combination with a bioactive agent, a composition which comprises vesicles formulated from a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety.

75. A composition for use in targeting an internal region of a patient having vascular plaque, wherein the composition comprises vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety.

76. A composition according to Claim 75 which comprises lipid vesicles.

77. A composition according to Claim 76 wherein said lipid comprises a phospholipid.

78. A composition according to Claim 77 wherein said phospholipid is selected from the group consisting of a phosphatidylcholine and a phosphatidylethanolamine.

79. A composition according to Claim 78 wherein said phosphatidylcholine is selected from the group consisting of dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

80. A composition according to Claim 79 wherein said phosphatidylcholine comprises dipalmitoylphosphatidylcholine.

81. A composition according to Claim 78 wherein said phosphatidylethanolamine is selected from the group consisting of dipalmitoyl-phosphatidylethanolamine, dioleoylphosphatidylethanolamine, N-succinyldioleoyl-phosphatidylethanolamine and 1-hexadecyl-2-palmitoylglycerophosphoethanolamine.

82. A composition according to Claim 81 wherein said phosphatidylethanolamine comprises dipalmitoylphosphatidylethanolamine.

83. A composition according to Claim 76 wherein said lipid further comprises a polymer.

84. A composition according to Claim 83 wherein said polymer comprises a hydrophilic polymer.

85. A composition according to Claim 84 wherein said polymer comprises polyethylene glycol.

86. A composition according to Claim 75 which comprises protein vesicles.

87. A composition according to Claim 86 wherein said protein comprises albumin.

88. A composition according to Claim 75 wherein said gas or gaseous precursor comprises a fluorinated compound.

89. A composition according to Claim 88 wherein said fluorinated compound is a perfluorocarbon compound.

90. A composition according to Claim 89 wherein said perfluorocarbon is selected from the group consisting of perfluoromethane, perfluoroethane,

perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane, perfluorohexane, perfluoroheptane, perfluorooctane, perfluorononane, perfluorodecane, perfluorodecalin, perfluoroundecane, perfluorododecane, and mixtures thereof.

91. A composition according to Claim 90 wherein said perfluorocarbon is selected from the group consisting of perfluoropropane, perfluorobutane, perfluorocyclobutane, perfluoropentane, perfluorohexane, and mixtures thereof.

92. A composition according to Claim 91 wherein said perfluorocarbon is perfluorobutane.

93. A composition according to Claim 75 wherein said targeting ligand comprises a lipid containing said acid moiety.

94. A composition according to Claim 93 wherein said targeting ligand comprises an acidic phospholipid.

95. A composition according to Claim 94 wherein said targeting ligand is a diacyl phospholipid.

96. A composition according to Claim 94 wherein said targeting ligand is selected from the group consisting of phosphatidic acids, phosphatidyl serines and phosphatidylinositols.

97. A composition according to Claim 96 wherein said targeting ligand is a phosphatidic acid which is dipalmitoylphosphatidic acid.

98. A composition according to Claim 96 wherein said targeting ligand is a phosphatidyl serine which is dipalmitoylphosphatidylserine.

99. A composition according to Claim 75 which further comprises a low viscosity oil.

100. A composition according to Claim 99 wherein said oil is selected from the group consisting of silicone oil, cod liver oil, mineral oil, triacetin, plant oil, oil comprising fluorinated triglycerides, biocompatible saturated fatty acids, biocompatible unsaturated fatty acids, biocompatible partially hydrogenated fatty acids, silicon-based oils, and synthetic oil.

101. A composition according to Claim 76 wherein said vesicles are selected from the group consisting of micelles and liposomes.

102. A composition according to Claim 101 wherein said lipid vesicles are selected from the group consisting of unilamellar lipid vesicles, oligolamellar lipid vesicles and multilamellar lipid vesicles.

103. A composition according to Claim 102 wherein said lipids are in the form of monolayers or bilayers.

104. A composition according to Claim 75 which further comprises a bioactive agent.

105. A composition according to Claim 104 wherein said bioactive agent is selected from the group consisting of anti-thrombolytic drugs, statins, anti-cancer agents, and radioactive materials.

106. A composition for use in targeting an internal region of a patient having vascular plaque, wherein the composition comprises vesicles formulated from a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety.

107. A formulation for therapeutic or diagnostic use in a patient having a vascular plaque, wherein the formulation comprises, in combination with a bioactive agent, a composition comprising vesicles formulated from a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety.

108. A formulation according to Claim 107 wherein said vesicles comprise lipid vesicles.

109. A formulation according to Claim 108 wherein said vesicles are selected from the group consisting of micelles and liposomes.

110. A formulation for therapeutic or diagnostic use in a patient having a vascular plaque, wherein the formulation comprises, in combination with a bioactive agent, a composition comprising vesicles formulated from a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety.

111. A process for the preparation of a composition for use in targeting a region in a patient having a vascular plaque, wherein the process comprises combining together a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety.

112. A process according to Claim 111 wherein said composition comprises vesicles.

113. A process for the preparation of a composition for use in targeting a region in a patient having a vascular plaque, wherein the process comprises combining together a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally,

an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety.

114. A process for the preparation of a formulation for therapeutic or diagnostic use in a patient having a vascular plaque, wherein the process comprises combining together a bioactive agent, a lipid or protein, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises an acid moiety.

115. A process according to Claim 114 wherein said formulation comprises lipid vesicles.

116. A process for the preparation of a formulation for therapeutic or diagnostic use in a patient having a vascular plaque, wherein the process comprises combining together a bioactive agent, a lipid or polymer, a gas or gaseous precursor, a targeting ligand, and optionally, an oil, wherein said targeting ligand targets cells or receptors associated with vascular plaque and comprises a phosphorylated serine moiety.